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TECHNICAL NOTE

The Influence of Homologous Blood Transfusion on Immunity and Clinical Outcome in Aortic Surgery

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Objectives: *to evaluate the influence of homologous blood transfusion on immune responses and post-operative morbidity in aortic surgery.*
Design: *analysis of the effects of homologous blood transfusion in 128 patients in a prospective randomised trial evaluating homologous and autologous blood transfusion in aortic surgery.*
Materials and methods: *blood sampled before and at five times after surgery was assayed for C-reactive protein (CRP), neutrophil elastase, TNF-α and IL-6. Transfusions, morbidity and mortality were recorded; factors associated with poor outcome were identified by logistic regression.*
Results: *homologous transfusion during surgery was required in 32 patients and precipitated an increase in neutrophil elastase ($p = 0.008$) and TNF-α ($p = 0.015$) but not IL-6 and CRP. Elastase peaked early in transfused patients at 41.27 (13.92–52.11) Δng/ml by 2 h compared to a peak of 21.51 (10.64–31.13) Δng/ml by 24 h in those who were not transfused. TNF-α peaked at 1.2 (0–4.33) Δpg/ml by wound closure in transfused patients and at −0.1 (−2.05–2.52) Δpg/ml by 2 h without transfusion. Intra-operative homologous transfusion was associated with increased mortality ($p = 0.01$) and prolonged intensive care stay ($p = 0.03$). Mortality increased with age ($p = 0.003$) and was inversely related to the CRP peak ($p = 0.007$). Prolonged surgery predicted post-operative complications ($p = 0.025$).*
Conclusion: *homologous transfusion increased the inflammatory response to aortic surgery and was associated with mortality.*

Key Words: Transfusion; Aortic surgery; Immune response; Morbidity and mortality.

Introduction

Elective surgery accounts for over 40% of all stored blood transfusions and an even greater proportion of cross-match requests.[1] Blood transfusion is life saving in severe haemorrhage, following trauma or as a complication of surgery and its benefits in these indications are undisputed. However, homologous blood transfusion was introduced before randomised clinical trials were widely adopted and its risks are only now being quantified. Homologous transfusion may induce a number of changes within the immune system, causing immuno-suppression and contributing to infectious complications.[2–4] Homologous blood has also been associated with a variety of transfusion reactions, graft-versus host disease, allo-immunisation, the transmission of infectious agents, and immunomodulation.[2,5,6] Immuno-suppression due to homologous blood may influence postoperative infection rates, prognosis in cancer and transplant rejection.[7–12] The precise mechanism of these immune effects has yet to be characterised but may be mediated by both cellular and humoral components.[13]

Autologous blood transfusion may avoid the immuno-suppression associated with homologous transfusion. A number of studies reported marked reductions in hospital infection rates, antibiotic usage and even length of hospital stay in patients offered autologous transfusion.[14–16] However, these studies were either not randomised, were retrospective or the numbers of patients involved were inadequate to influence transfusion policy. In a meta-analysis of seven clinical trials on 1060 patients, the risk of post-operative infection was 2.37 times greater for patients receiving homologous blood.[12]

We investigated the effect of homologous blood transfusion on inflammatory response and clinical outcome in patients recruited into a randomised clinical

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Table 1. Inclusion and exclusion criteria.

Inclusion	Exclusion
Elective infra-renal aortic reconstruction	Myocardial infarction in the previous 6 months
Age >30 and <85 years	Severe angina (American Heart Society)
Hb >110 g/L	Myocardial ischaemia on resting ECG
Platelet count >150 000/L	Aortic stenosis
Written informed consent	Cardiac ejection fraction <40%
	Pre-operative creatinine >200 mmol/L
	Aspartate amino-transferase >100 iu/L
	Patient refusal of homologous blood
	Blood disorders excluding either transfusion technique
	Severe pulmonary disease (PaO_2 <9 kpa on air; FEV_1 <50% predicted)

trial comparing two different blood transfusion strategies: autologous versus homologous transfusion when necessary. The main clinical findings of this trial have been reported elsewhere.[17] We now report the results in relation to intraoperative homologous blood transfusion requirement.

Materials and Methods

Patients

Following ethical approval and fully informed consent, 128 patients were randomised to either autologous (acute normovolaemic haemodilution and intraoperative cell salvage, $n=65$) or homologous ($n=63$) transfusion before elective aortic surgery from June 1997 to July 1999. Table 1 describes the inclusion and exclusion criteria. There were eight participating hospitals but randomisation was central, by computer in the Vascular Studies Unit at South Manchester University Hospital. Allocation was stratified using minimisation for (i) hospital, (ii) aortic disease (aneurysm or occlusive), (iii) anti-platelet or anti-coagulant drugs and (iv) estimated blood volume.

Anaesthetic technique

Standard general anaesthetic techniques were used with intravenous induction, endotracheal intubation and intermittent positive pressure ventilation. Maintenance of anaesthesia was by either an intravenous or a volatile agent with intraoperative fluids limited to crystalloids where possible. Colloids were avoided due to their possible effect on the acute phase response. Epidural anaesthesia with local anaesthetic drugs was delayed to the postoperative period to avoid expanding the intravascular volume, causing further haemodilution.

Transfusion triggers

Homologous blood was administered when the haemoglobin concentration fell below 80 g/L, unless salvaged red cells were available. Intraoperatively, transfusion could also be administered when abnormal vital signs or ischaemic electrocardiographic changes persisted after correction of hypovolaemia or in case of severe haemorrhage.

Autologous transfusion

Patients randomised to autologous transfusion underwent acute normovolaemic haemodilution after induction of anaesthesia and immediately before surgery. The amount of blood removed was based on the preoperative haemoglobin concentration and estimated blood volume calculated from published nomograms, aiming for a post-haemodilution haemoglobin of 105–110 g/L.[18,19] Cell salvage was by centrifugal devices (Cell saver 5, Haemonetics, U.K. or Brat 2, Cobe Laboratories, U.K.). All autologous blood was re-infused within 6 h of collection.

Inflammatory mediators

Peripheral venous blood was sampled into standard serum and EDTA blood tubes at six time points: (i) preoperatively, and postoperatively at (ii) wound closure, (iii) 2 h, (iv) day one, (v) day two and (vi) day seven. This was immediately centrifuged at 1300 g for 10 min and plasma/serum samples transferred to −80 °C storage for subsequent analysis. C-reactive protein (CRP) was analysed by a standard turbidometric procedure (Dako, Nycomed, Ely, U.K.). Plasma samples were used to assess neutrophil elastase using an "in house" enzyme-linked immunosorbent assay, according to the method of Brower and Harpel.[20]

Table 2. Patients details.

	Intraoperative homologous transfusion		
	No ($n=96$)	Yes ($n=32$)	p
Median age (IQR)	70 (66–76) years	70 (64–75) years	n.s.
Sex (male/female)	80/16	24/8	n.s.
Disease (aneurysm/occlusive)	67/29	27/5	n.s.
Co-morbidities			
Cardiac	34 (35%)	12 (37.5%)	n.s.
Respiratory	21 (22%)	9 (28%)	n.s.
Hypertension	36 (37%)	14 (44%)	n.s.
Diabetes	2	0	n.s.
Smoking habit			
Yes	25 (26%)	10 (31%)	n.s.
No	11 (11%)	4 (12.5%)	n.s.
Ex	60 (63%)	18 (66.5%)	n.s.
Median aneurysm size (IQR)	6 (5.5–7) cm	6.4 (5.6–7) cm	n.s.
Randomisation (autologous/homologous)	58/38 (60%)	7/25 (22%)	<0.001

IL-6 and TNF-α were measured in serum samples using commercially available paired antibodies (Biosource, Lifescreen Ltd, Harefield, U.K.). Assays were optimised for serum samples to ensure reproducibility and were sensitive to cytokine concentrations lower than 5 pg/ml.

Statistical analysis

As all continuous variables were skewed, the Mann–Whitney *U*-test was used. The chi-squared test, with the Yates correction where appropriate, was used for proportions. To avoid multiple comparisons at different time points mediator concentration changes were summarised calculating the area under the curve (AUCs) for each subject. Correlations were calculated using the Spearman rank correlation coefficient. Backward stepwise multiple logistic regression was used to identify predictors of mortality, morbidity and postoperative infection. Co-variates in this analysis were peaks of mediators concentration, number of preoperative co-morbidities (cardiac disease, respiratory disease, hypertension and diabetes), age, aortic disease (aneurysm or occlusive), transfusion strategy (autologous or homologous), blood loss, operating time and number of homologous units transfused during surgery. In this analysis, continuous variables were categorised around the median value.

Results

The study population was typical of any cohort of patients undergoing aortic surgery (Table 2).

Transfusion

Thirty-two patients required intraoperative transfusion of a median (IQR) of 2 (2–4) homologous units. One-hundred-and-fourteen of the 119 transfusions were buffy coat poor red cell units and the remaining five were whole blood units. Transfused patients had a significantly higher median (IQR) blood loss of 1742 (1102–2825) ml compared to 800 (580–1169) ml ($p<0.001$) as estimated by blood lost to suction and swab weight. They also received more intravenous fluids during surgery at a median (IQR) of 4450 (3750–5075) ml compared to 3500 (3000–4500) ml in patients who were not transfused ($p<0.001$). Randomisation to "autologous" reduced the need for homologous blood during surgery from 25/63 (40%) to 7/65 (11%) ($p<0.001$).

Clinical outcome

Mortality and morbidity for the duration of the inpatient stay are summarised in Table 3. Intensive care was required more frequently for transfused patients, with a median intensive care unit stay (IQR) of 1 (1–2) days compared to 1 (1–1) days in patients who were not transfused ($p=0.03$).

Inflammatory mediators

As expected, there was a marked inflammatory response to surgery, and this was enhanced by intraoperative transfusion. The rise in neutrophil elastase

Table 3. Postoperative complications.

	Intraoperative homologous transfusion		
	No ($n=96$)	Yes ($n=32$)	p
Deaths	13 (13.5%)	10 (31%)	0.046
Cardiac	14 (15%)	6 (19%)	n.s.
Respiratory (not infective)	1 (1%)	3 (10%)	n.s.
Respiratory infection	20 (21%)	6 (19%)	n.s.
Graft thrombosis	9 (10%)	3 (10%)	n.s.
Haemorrhage	4 (4%)	7 (22%)	0.006
Renal	8 (8%)	5 (16%)	n.s.
Multiorgan failure	2 (2%)	5 (16%)	0.014
Other	8 (8%)*	7 (22%)†	

* Includes two wound haematomas, two groin wound infections, four intestinal complications.
† Includes one wound haematoma, one groin wound infection, two cases of urinary retention, two urinary tract infections, two intestinal complications, one deep vein thrombosis, one minor stroke.

was more pronounced in patients requiring intra-operative transfusion, with an earlier median (IQR) peak at 2 h of 80 (67–94) ng/ml compared to 58 (44–72) ng/ml. The volume of blood transfused during surgery correlated with the rise in neutrophil elastase at wound closure ($r=0.26$, $p=0.005$) and at 2 h ($r=0.31$, $p=0.001$). Neutrophil elastase remained elevated for a week after surgery in transfused cases, with a median (IQR) concentration of 65 (41–88) ng/ml compared to 46 (40–63) ng/ml in non-transfused patients a week following surgery. TNF-α increased to a median (IQR) 5 (3–13) pg/ml at wound closure following transfusion but, despite the insult of aortic surgery, did not rise substantially without transfusion. The rise in TNF-α at wound closure also correlated with the volume of homologous blood transfused ($r=0.4$; $p<0.001$). Median TNF-α concentration fell below baseline in most patients after the first postoperative day, regardless of transfusion. The IL-6 peak tended to occur earlier at 55 (24–164) pg/ml at 2 h in those requiring homologous blood during surgery, compared to 45 (20–112) pg/ml at 24 h in those not transfused. IL-6 returned towards normal by day two. CRP trends were similar in the two groups, with peaks at 48 h of 178 (132–228) and 162 (102–200) mg/L in transfused and non-transfused patients respectively. Median CRP concentration returned to baseline on day seven in both groups.

Randomisation to autologous transfusion had no significant influence on the concentration of neutrophil elastase ($p=0.67$), TNF-α ($p=0.34$), IL-6 ($p=0.21$) or CRP ($p=0.4$). TNF-α peaked at 2 h at 6 (3–17) pg/ml in "autologous" and 5 (2–14) pg/ml in "homologous" patients. The neutrophil elastase peak at day 1 was 66 (53–97) ng/ml in "autologous" and 63 (50–80) ng/ml in "homologous". IL-6 also reached its highest concentration 24 h following surgery at 73 (24–157) pg/ml in "autologous" and 47 (19–127) pg/ml in the "homologous" group. CRP peaked later, at 2 days, and was 165 (102–194) mg/L in "autologous" and 165 (111–227) mg/L in "homologous" patients.

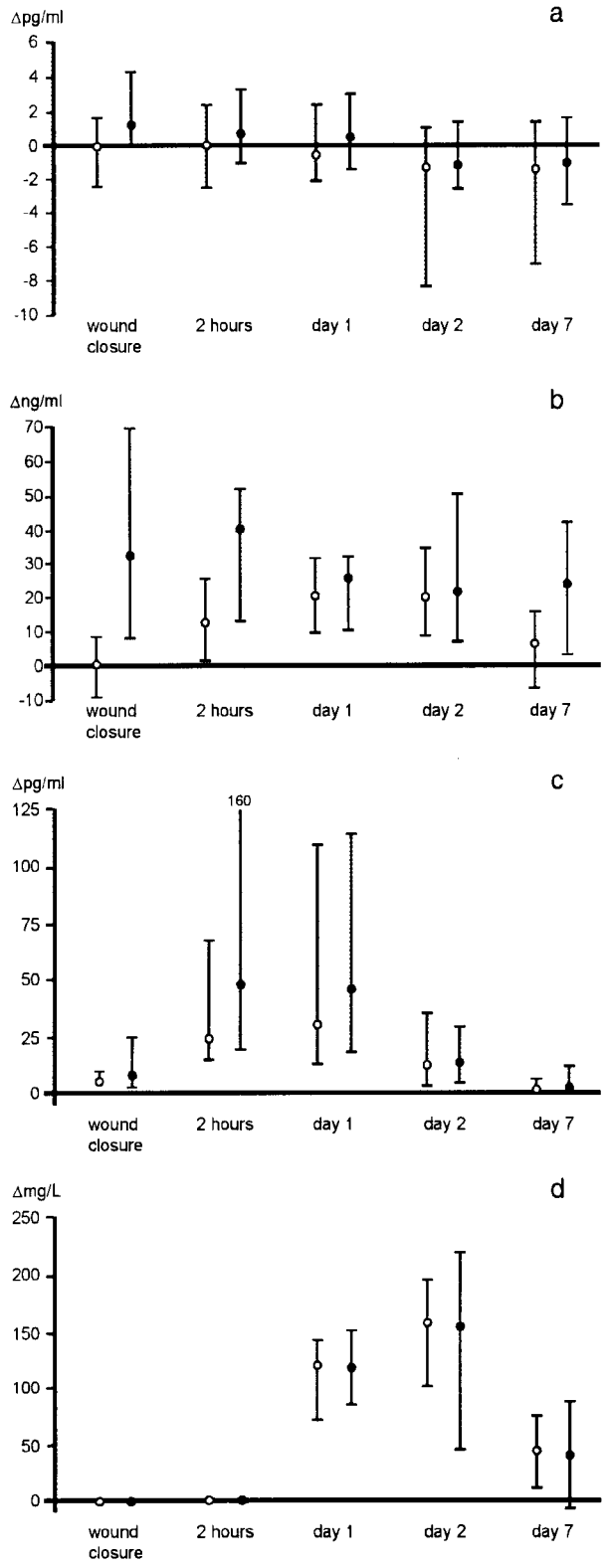
Predictors of poor outcome

Multiple logistic regression (Table 4) identified operating time >150 min as the only independent predictor of postoperative complications ($p=0.025$). Prolonged surgery (>150 min) also had a weak relationship with postoperative infections, with an OR (95% CI) = 1.5 (0.65–3.66) ($p=0.06$). The volume of intraoperative homologous transfusion in units was independently related to mortality on regression ($p=0.03$). Other predictors of mortality were age ($p=0.003$) and a CRP peak <158 mg/L ($p=0.007$). The median (IQR) CRP concentration at 48 h in patients who subsequently died was 124 (0–185) mg/L compared to 173 (136–212) mg/L in survivors ($p=0.01$). Preoperative co-morbidities, blood loss, aortic disease, randomisation to either transfusion strategy, neutrophil elastase, TNF-α and IL-6 did not predict clinical outcome.

Discussion

Elective aortic reconstruction generated a profound inflammatory response, amplified by intra-operative transfusion of stored blood. Exposure to homologous blood increased intensive care stays and, after adjustment for confounding variables, mortality. No statistically significant influence of transfusion on postoperative infection was detected in these patients undergoing clean surgery.

Previous work has shown that TNF-α and IL-6 rise in response to surgical trauma[21] and that, in ischaemia-reperfusion injury, TNF-α may mediate neutrophil



accumulation and priming, with levels rising after aortic cross-clamping and falling quickly after clamp removal.[22] Large increases in TNF-α have been associated with severe complications such as multi-organ failure,[23] but this finding was not confirmed by our data. In general TNF-α levels were not greatly increased in our elective surgery patients with many assays at the lower limit of sensitivity. Greater rises may have occurred transiently during surgery, recovering by the time blood was sampled after surgery. Elevated postoperative TNF-α was associated with intraoperative homologous transfusion but there was no significant correlation between TNF-α and morbidity.

IL-6 is a marker of tissue injury and systemic IL-6 responses reflect the severity of surgery.[24–26] We demonstrated an IL-6 peak within the first 24 h after surgery and a sharp fall over the next two days, which is consistent with previous reports.[27] IL-6 is thought to play a role in the induction of CRP synthesis: CRP peaked 24 h following the IL-6 response, but neither mediator was significantly influenced by homologous transfusion.

Increased neutrophil elastase following surgery has been related to postoperative complications and may reflect the overall immune response.[28] This increase was greater in our transfused patients but did not predict poor outcome. Neutrophil elastase and TNF-α concentrations are known to be increased in stored blood.[28,29] The increases we measured following surgery were related to the volume of homologous blood given during surgery and may be partly explained by the direct infusion of mediators.

Recently, homologous transfusion has been associated with increased postoperative mortality in colorectal,[30] pulmonary[31] and biliary[32] surgery. This association has not been reported in aortic surgery. In our multivariate model, we included measures of patient fitness (age, co-morbidities) and severity of surgery (aortic disease, blood loss, operating time) to verify this association. Although our results confirm a direct relationship between intraoperative transfusion and mortality, it remains impossible to distinguish entirely the effect of transfusion from the effect of the clinical conditions leading to transfusion. Mortality in this study was also suprisingly high, with significant variation among participating centres. This would tend to reduce our ability to detect effects due to blood

Fig. 1. Rises in inflammatory mediators in 32 transfused (●) and 96 non-transfused (○) patients. Rises in TNF-α (a) and neutrophil elastase (b) were more pronounced after transfusion ($p=0.015$ and $p=0.008$ respectively). There were no significant differences in IL-6 (c) and CRP (d). Values are medians and interquartile range.

Table 4. Perioperative predictors of mortality and complications.

	Odds ratio	95% CI	*p*
Mortality			
Homologous transfusion (units)	1.7	1.1/2.6	0.01
CRP peak <158 mg/L	5.8	1.6/20.6	0.007
Age (10 years increase)	3.9	1.6/9.3	0.003
Complications			
Operating time >2.5 h	3.1	1.5/6.5	0.025

transfusion alone; we were unable to demonstrate a protective effect for autologous transfusion on postoperative outcome. Intraoperative homologous transfusion was also associated with increased intensive care requirements but, in contrast to the published literature, there was no increase in postoperative infections. As expected, postoperative complications were predicted by operating time, which probably indicates difficult or complicated surgery.

A reduced CRP response to surgery predicted morbidity in our patients. Perhaps a generally dampened inflammatory reaction might enhance susceptibility to complications, but the clinical significance of this finding is uncertain. Many patients developed complications before CRP peaked at 48 h, and it is likely that the CRP response follows rather than precedes postoperative complications.

Our results confirm that postoperative inflammatory responses and outcome are influenced by homologous transfusion. The mechanism leading to these changes remains uncertain. Although autologous transfusion failed to influence post-operative outcome in this study, further research involving greater numbers of patients is needed to clarify its influence on morbidity and mortality.

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